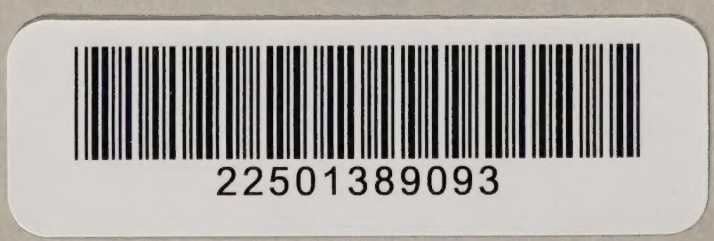
VITAMIN B1 THERAPY

with 'Betaxan'

OCT 1937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Vitamin B1 Therapy

with
'Betaxan'

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GENERAL SUMMARY AND ARGUMENT

¶ Vitamin B 1—one of six or seven factors comprising the 'Vitamin B Complex.'

¶ History of the discovery of vitamin B 1 dates from observations made by Admiral Takaki in 1878; was pursued by Eijkmann and others, and culminates in its successful synthesis by Andersag and Westphal in 1936.

¶ Resultant product—Betaxan—identical with natural vitamin B 1.

¶ Vitamin B 1 widely distributed in animal and vegetable worlds, but only in very small quantities, richest sources being yeast and the germs of cereals.

¶ Modern methods of preparing cereals robs them of vitamin B 1 content: losses also occur during cooking of foods and as a result of preservation.

¶ Vitamin B 1 content of typical foods is tabulated.

¶ Chemical and physical characters and structural formula.

¶ Vitamin B 1 an essential agent in carbohydrate metabolism, exerting a catalytic action in the ultimate breakdown of ketonic acids.

¶ International, Sherman-Chase, and Pigeon Units defined. These units now superfluous since precise chemical constitution determined and synthesis achieved.

¶ Equivalents of different units.

¶ Variation of daily requirements of vitamin B 1 in accordance with carbohydrate consumption and metabolic changes. Requirement raised in exercise, hyperthyroidism, fevers, pregnancy, and lactation.

¶ Average requirement of adults probably in the neighbourhood of 1 mgm. per day.

¶ Entire freedom from danger of overdosage of vitamin B 1. Minimum toxic dose 7,200 times therapeutic dose.

¶ Hypovitaminosis-B 1. Occurs in most severe form in the East as *Beri-Beri.* Favourable results of early treatment with vitamin B 1.

¶ In temperate countries *minor degrees of hypovitaminosis*-B 1 due to actual lack of vitamin in diet, increase in bodily requirement, failure of assimilation, or a combination of two or more of these factors.

¶ Lack of appetite and under-development in children corrected by therapeutic administration of vitamin B 1.

¶ Symptoms of minor deficiency in adults include *anorexia, constipation, asthenia, breathlessness, œdema,* and *neuritis* or *neuralgia.*

¶ Danger of deficiency in special *diets* (in treatment of *peptic ulcer, obesity*), also in *pregnancy and lactation,* owing to greatly increased requirements which the diet is unable to support. (In nursing mothers 60 per cent. of B 1 intake lost in the milk.)

¶ *Polyneuritis of pregnancy* due to B 1 deficiency. Success of treatment by parenteral administration of Betaxan.

¶ Alcoholic polyneuritis now known to be due to defective absorption of vitamin B 1 from the alimentary tract. Alleviated by Betaxan injections (without limitation of alcohol).

¶ Methods of estimating B 1 deficiencies.

¶ Effect of B 1-free diet in depleting tissue-reserves shown by lag in urinary output of the vitamin when B 1-rich diet substituted.

¶ Therapeutic applications of Betaxan in other conditions. *Polyneuritis and localised Peripheral Neuritis of unknown œtiology. Neuritis* due to poisoning *from Heavy Metals. Occupational Neuritis. Post-Influenzal Neuritis. Sciatica. Post-Diphtheritic Palsies. Trigeminal Neuralgia. Intercostal Neuralgia.* Neuritic pains in *Tabes Dorsalis. Sub-Acute Combined Degeneration. Disseminated Sclerosis. Delayed Union of Fractures.* Irreversible *Coma in Insulin Shock. Certain cases of Œdema. Rheumatism* associated with Anorexia. *Gastro-Enteritis.*

¶ Classified summary of clinical indications.

¶ Administration and Dosage.

¶ Alphabetical Index of Indications.

"THE VITAMIN B COMPLEX"

Although within recent years considerable advances have been made, contemporary knowledge of the various factors comprising the vitamin B complex is still far from complete. It is thought that there are at least six or seven of these factors which are enumerated below :—

VITAMIN B 1. (Synonyms. Aneurin. Torulin. Oryzanin. Vitamin F. Known in the American literature as Vitamin B). The anti-neuritic vitamin.

VITAMIN B 2. (Vitamin G). A flavine compound promoting growth in the rat.

VITAMIN B 3. A factor essential to the maintenance of weight in pigeons and chickens.

VITAMIN B 4. Little is known of this factor and its existence is questioned by some. It has been reported that its absence from the diet of rats results in a muscular weakness associated with spasticity.

VITAMIN B 5. Differs from B 1 and B 3 in that it is less thermolabile. Necessary for the maintenance of weight in pigeons.

VITAMIN B 6. Absence of this Vitamin from the diet of rats results in dermatitis.

P.P. BODY. Deficiency of this factor is productive of human pellagra. May or may not be identical with a factor the absence of which causes black tongue in dogs or with the substance preventing pellagra in chickens.

Of the components of the complex more is known of Vitamin B 1 than of any of the others. It is this factor which is the subject of this treatise.

HISTORY

The effects of an insufficient intake of Vitamin B 1 became manifested on a large scale in the East following the introduction of hulled rice. These effects constituted a syndrome which received the name of ' beri-beri,' in which a multiple peripheral neuritis was associated with profound nutritional and cardio-vascular disturbances.

As early as 1878, Admiral Takaki had recognised an association between the rice diet and the incidence of beri-beri in the Japanese Navy.

In 1897 Christian Eijkmann, while stationed at a hospital in Java, observed that chickens fed on polished rice developed a polyneuritis which he regarded as similar to beri-beri in human beings. He made the further important observation that this polyneuritis in chickens could be cured and prevented by the addition of rice-husks to their diet. Applying his conclusions to human beings, he found an excellent field for study in the prisons of the Dutch East Indies where, owing to variations in local customs, different methods of preparing rice prevailed. From observations, which involved over a quarter of a million individuals, Eijkmann compiled statistics which showed the percentage incidence of beri-beri to be 0.01 where the diet consisted of unpolished rice, 4.16 where a mixture of polished and unpolished rice was eaten, and 39 among those who consumed only polished rice. The natural consequence of these findings, the implications of which were subsequently confirmed by numerous other observers, was the administration of extracts of

rice-husks to sufferers from beri-beri, a treatment which was adopted on a large scale by the Philippine Government who, in 1914, authorised the free distribution of rice-husk extracts to nursing mothers and infants in cases of infantile beri-beri. This policy was fully justified by the results which it produced.

It was not until 1919 that it was first suggested in a paper by H. H. Mitchell, that the accessory food substance which had by then become known as Vitamin B might be not a single entity but a complex of two or more factors.

In 1927, a further advance was made when Jansen and Donath isolated the antineuritic vitamin in pure crystalline form from rice polishings. In 1931, as a result of the collaboration of the Institute of Chemistry of the University of Göttingen and the Bayer Research Laboratories in Elberfeld, the same active principle was for the first time isolated from yeast.

The final stage was achieved in 1936 by Andersag and Westphal, who established the structural formula of Vitamin B 1 and shortly afterwards synthetised it. The resultant product, Betaxan, is identical in every respect, chemically and biologically, with the crystalline vitamin B 1 extracted from natural sources.

NATURAL SOURCES OF VITAMIN B 1

The Vitamin B complex is widely distributed in the plant world in varying quantities, the germ of cereals and yeast furnishing the most concentrated sources. The animal organism, however, is unable to synthetise Vitamin B, or to store it for more than a short period. Foods of animal origin, therefore, are not rich in Vitamin B, with the exception of lean pork, pancreas, liver, milk and eggs.

With the introduction of modern refining processes in the preparation of the cereals, a serious depletion of their Vitamin B content has occurred, white bread and polished rice, for example, containing only negligible quantities.

A further important consideration is that a marked loss of the vitamin is apt to occur in the domestic preparation of foodstuffs owing to its solubility in water. In addition to this loss, there may be actual destruction of the vitamin caused by the combination of heat and alkalinity which results from the common practice of adding sodium bicarbonate to the water in which vegetables are boiled. It has also been found that the Vitamin B content of preserved foods tends to undergo a progressive diminution.

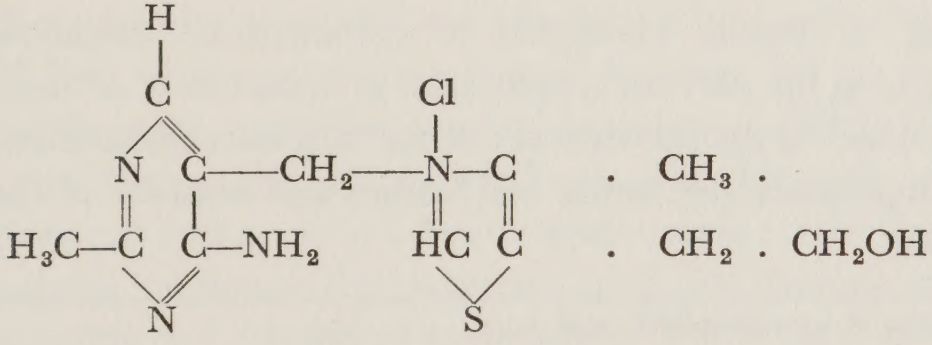
The following table indicates the relative adequacy of various foods as sources of Vitamin B 1. The figures represent 'international units' per ounce of food. (Eddy and Dalldorf, 1937).

Apples	21	Eggs	7–8	Potatoes	6
Asparagus, Green	50–275	Fish	4–14	Prunes	7–20
Bacon	25	Kidney	12	Rice, White	2
Beans	20–50	Leeks	7–14	Rice, Polishings	84–116
Bread, White	3	Lettuce	5	Spinach	8–15
Bread, Whole Wheat	22	Liver	14	Tomatoes	4–5
Butter	11	Milk	3–7	Wheat Germ	169–500
Celery	3	Oats	19–34	Yeast, Dried Brewers	49–420
Cheese	3	Oranges	8		
Cucumber	5	Pork, Lean	7–14		

It may be noted that one ounce of Betaxan represents 15,000,000 international units. Expressed in less astronomical figures, one ampoule of Betaxan (containing 2 mgm. Vitamin B 1) represents approximately 1,000 international units.

CHEMICAL AND PHYSICAL CHARACTERS

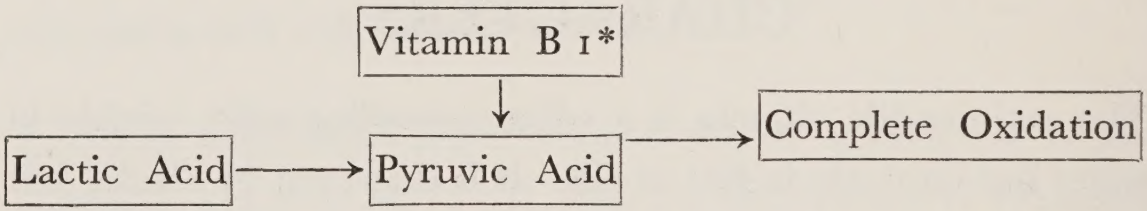
The anti-neuritic vitamin is a white crystalline solid, soluble in water but insoluble in fats or oils. It is destroyed by alkalis, but resists the action of weak acids. It withstands heating to 100° Centigrade for several hours in neutral or acid solutions, but is destroyed at a temperature of more than 120°. Chemically, it is a combination of a pyrimidine base and a thiazol ring, and it is represented by the following structural formula :—



FUNCTIONS OF VITAMIN B 1

Vitamin B 1 is known to be necessary for the maintenance of life and to prevent and cure the characteristic manifestations of beri-beri. It has been found that it plays an essential part in the processes of tissue oxidation and carbohydrate metabolism. (Peters, 1936).

According to Lohmann's work, Vitamin B 1 has an important role in the intermediate stage of break-down of the ketonic acids, especially pyruvic acid. This is demonstrated by the fact that the pyrophosphoric acid ester of Vitamin B 1 is identical with co-carboxylase, which is an important catalyst in metabolism. Should the vitamin be lacking, the process is arrested at the stage of the production of pyruvic acid. This mechanism may be represented diagrammatically :—



Recent experimental observations on human beings have lent strong confirmation to this view. Analyses of the blood of patients suffering from severe beri-beri showed a great increase in the level of lactic acid and pyruvate in the blood. (Platt and Lu, 1936, et alia.).

According to Peters, anomalies of carbohydrate metabolism, particularly in the nervous system, lead to impairment of function of the neurones of the subcortical centres with consequent disorder of the temperature regulating mechanism and disorder of tissue-metabolism.

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* In the form of pyrophosphoric acid ester.

STANDARDISATION OF VITAMIN B 1

In 1931 the Vitamin Committee of the League of Nations provisionally adopted as standard a preparation of Vitamin B 1, which was adsorbed by Fuller's Earth. Ten milligrammes of this adsorption-product constituted one international unit.

The activity of Vitamin B 1 can only be measured by biological methods, that is by comparison of the activity of an unknown preparation with that of a known standard, for example, the international standard. Of the various methods of biological standardisation—i.e., the aforementioned comparison—those of (1) Sherman-Chase and (2) Peters are the most commonly used. The method of Harris and Leong (see p. 15) is another example.

The Sherman-Chase unit is defined as the amount of Vitamin B 1 which, added to Vitamin B 1-free diet, produces a weekly gain of weight in the rat amounting to 3 grammes. The unit employed by Peters the 'pigeon unit', is defined as the amount of Vitamin B 1 necessary to keep a pigeon free from signs of deficiency for 24 hours. In actual fact, one pigeon unit equals 0·0025 milligrammes of the pure vitamin.

It is to be hoped that the successful synthesis of the vitamin, the practical outcome of which is the Bayer preparation, Betaxan will render the continued use of these various units obsolete, and will lead to the standardisation of Vitamin B 1 by comparison with the pure crystalline synthetic substance. While it may well be that the present international unit will ultimately be replaced by the establishment of a figure representing a unit weight of the synthetic substance (for example, 2 γ), the various methods of estimating B 1 are still of some value. Peters' method is used in

the laboratory for examining the specificity of a supposed Vitamin B 1-like substance. The rat-feeding method is of value for accurate estimation, while another method which involves the catalytic action of the vitamin upon the rate of growth of a mould, *Phycomyces blakesleeanus* is employed owing to its extreme sensitivity.

Our own packings of Vitamin B 1 are standardised in weight of the synthetic crystalline substance. Each ampoule contains 2 milligrammes of the pure synthetic substance per c.c. with the exception of the so-called 'forte' ampoules which contain 10 milligrammes per c.c. Tablets for oral use contain 1 milligramme per tablet.

It is frequently asked whether the exact equivalents can be given for the various units of Vitamin B 1, which are referred to in the literature and on the packings of commercial preparations. Unfortunately there does not appear to be any unanimity of opinion regarding the relationships of these different units. For practical purposes, however, it is possible to give the following *rough* figures :

1 milligramme of synthetic crystalline Vitamin B 1 (Betaxan)= 400 pigeon units=400 Sherman units=**500 International Units.**

DAILY REQUIREMENT

The daily quantity of Vitamin B 1 in the diet necessary for the maintenance of health is not an absolute constant. There is an approximate mathematical relationship between the quantity of carbohydrate consumed and the amount of vitamin B 1 required. (Cowgill, 1934). The need of the body for Vitamin B 1 increases as the carbohydrate consumption rises, so that without the simultaneous administration of Vitamin B 1 very large quantities of carbohydrates may produce toxic effects. Nevertheless, even where the dietary is adequate, a relative B 1-avitaminosis may occur in conditions where an enhanced rate of metabolism calls for an additional supply of the vitamin. Prolonged muscular exertion, increased activity of the thyroid gland, and febrile diseases are examples of such conditions. In addition, the daily Vitamin B 1 requirement is greatly increased in pregnancy and actation, and a relative deficiency may—and often does—occur at these times.

The ordinary requirements of the Vitamin in the adult have been calculated as a minimum of 1 milligramme per day ; during pregnancy and lactation this may be raised to five times this amount.

Harris and Leong (1936) regard two hundred International units (roughly 0·4 mg. Betaxan) as the *minimal* allowance for a man weighing ten stone.

Furthermore, it has been shown that beri-beri may occur on a diet including four hundred or more International units. (Baker, 1936). It should be noted that the daily requirement of infants is relatively much higher in proportion to their weight, than that of adults. In view of these considerations it would seem advisable to err on the side of generosity in estimating the optimum Vitamin B 1 value in any dietary.

EFFECTS OF EXCESSIVE INTAKE

The available evidence points to the conclusion that, although a sub-optimal Vitamin B 1 income readily gives rise to symptoms, excessive quantities are most unlikely to produce harmful effects. Peters (1937) has written : ' There seems to be no danger of over-dosage,' while Eddy and Dalldorf (1937) assert that ' there is no evidence of harmful effects from excess of Vitamin B.'*

Again, Hecht and Weese (1937) endeavoured to produce a state of hypervitaminosis B 1 in Macacus Rhesus monkeys, in which the therapeutic dose varies from 1/60 to 1/12 mgm. per kgm. body-weight. They found that repeated doses of 100—200 mgm. per kgm. administered over a long period failed to produce any evidence of cumulative effects. With single doses of 600—700 mgm. per kgm. toxic reactions were observed which lasted for about an hour, after which the animals fully recovered. Even doses of 1 gm. per kgm. failed to result in death. *These figures show a therapeutic ratio which entirely obviates any danger of over-dosage, the minimum toxic dose amounting to 7,200 times the therapeutic dose.*

*B 1 in the European terminology.

CLINICAL SECTION

HYPOVITAMINOSIS B 1

A. *Beri-beri.* (*Polyneuritis Endemica. Hydrops Asthmaticus. Kakke.*) Beri-beri is endemic in India, Malaya, Japan, the East Indies, and the Philippines. Its geographical distribution is determined by the fact that, in these regions, the population subsists almost entirely on polished rice.

Beri-beri also occurs in Newfoundland and Labrador, where white flour forms a large part of the dietary, and in the sailing ships of the Western Ocean in which the bulk of the food is, of necessity, preserved.

The disease has an incubation period of two to three months, and its onset is manifested by anorexia, epigastric discomfort, general weakness and constipation. Later, the symptoms of a multiple peripheral neuritis develop, with tenderness of the calves, paræsthesiæ, and patches of hyperæthesia and anæthesia. Should the autonomic nervous system be involved the innervation of the heart is affected, and dyspnœa, palpitations and tachycardia result.

In the 'wet' form of beri-beri œdema is a conspicuous sign. Examination of the blood reveals a considerable rise in the blood-sugar level. Post-mortem findings include a Wallerian degeneration in the peripheral nerves, stigmata of degeneration in the autonomic nerves, congestion of the gastric and duodenal mucosa, and degenerative changes in the myocardium.

Early treatment by the administration of Vitamin B 1 and a low carbo-hydrate diet results in a progressive improvement terminating in cure.

B. Minor States.

Of recent years it has become increasingly recognised that minor degrees of hypovitaminosis B 1 may occur in temperate countries and may be co-existent with an apparently full diet.

Peters (1937) asserts : ' the statement commonly made that because an individual eats a good mixed diet he cannot be suffering from vitamin deficiency is mere dogmatism.' He adds that : ' as a general symptom of vitamin lack, probably failure of appetite is the most important, and the most important vitamin in this connection is Vitamin B 1.'

Vorhaus, Williams and Waterman (1935) have stated that there is evidence to show that relative lack of Vitamin B 1 is of common occurrence, and that minor degrees of this deficiency are rarely recognised clinically.

Three factors, operating either singly or in conjunction, may be responsible for the occurrence of hypovitaminosis B 1 :

1. Poverty of Vitamin B 1 in the diet.
2. Increase of Vitamin B 1 requirement.
3. Failure to assimilate Vitamin B 1.

Infants and children with a poor appetite who fail to maintain the normal rate of growth and general nutrition are not infrequently suffering from the effects of a deficient Vitamin B 1 income, and they improve rapidly when the deficiency is corrected. In adults, the most constant symptoms of this dietary inadequacy are anorexia and constipation. These may be associated with suboptimal weight, muscular hypotonia, dyspnœa and palpitations, a fall in blood-pressure, œdema, and neuritic or neuralgic pains.

Professor Peters (1936), who has been intimately associated with the development of research on Vitamin B 1 in this country, has advocated its clinical use : ' in conditions of loss of appetite with œdema, palpitations and breathlessness, especially where there is a defective removal of blood lactic acid after exercise,

neuritic conditions and painful muscles.' The same authority states as his considered opinion that in every case of failure of appetite, the Vitamin B 1 content of the diet should be considered with a view to correcting any inadequacy. He adds that ordinary sources of the Vitamin are too dilute for use in remedying the defect and that a concentrated preparation should be given.

Vorhaus, Williams and Waterman (1935) describe the symptoms of moderate deficiency as including ' localised persistent pain, usually in an extremity or in the back and anorexia.' Paræsthesia is frequently present. There is little or no weakness. This condition is usually associated with obesity and a disturbed carbohydrate metabolism. It is frequently classified as a '*diabetic or metabolic neuritis*.' They also describe a lesser degree of deficiency characterised by ' vague pains, usually only elicited by pressure over the nerve roots, general malaise, anorexia, and constipation. Small amounts of sugar may be present in the urine without hyperglycæmia.'

An inadequate intake of Vitamin B 1 is particularly prone to occur where a special diet has been ordered, as in the treatment *of obesity or of gastric or duodenal ulcer.* In such cases it is advisable to supplement the diet by giving some preparation of the vitamin.

In the *pregnant and lactating woman* the requirement of Vitamin B 1 is raised considerably, and in the nursing mother it is of particular importance to ensure an adequate supply, as it has been estimated (Sure, 1928) that 60 per cent. of the daily intake is lost in the milk. It has been suggested also that a B 1-deficient diet may contribute to a failure in lactation, while Balfour (1931) found a marked deficiency of this vitamin in the diets of women who had given birth to premature infants. *Polyneuritis of preg-*

nancy has now been shown to be due to a B 1-deficiency (Strauss and McDonald, 1933), for which the increased utilisation of the vitamin during gestation and the interference with its absorption due to vomiting are each partially responsible.

Theobald (1936) cites five cases of polyneuritis in pregnancy successfully treated by a combination of oral and parenteral administration of Vitamin B 1.

Stahler (1937) has noted the effects of hypovitaminosis B 1 in a series of fifteen pregnant women. The deficiency was due either to an inadequate diet or to digestive disturbances or to a combination of both. Patients complained of numbness of the hands and feet and paræsthesiæ in the limbs. In 10 cases there was œdema without existing renal disease. In mild cases, oral administration was found to be satisfactory, but in the more severe types, parenteral administration was necessary.

Widenbauer (1936) describes a case in which *vomiting of pregnancy* and an unsuitable diet combined to produce a severe hypovitaminosis B 1. In addition to symptoms of exhaustion, sweats, dyspnœa, and a sense of oppression and pains in the precordial region, the patient complained of a 'furry feeling' in the finger tips and the soles of the feet, numbness of the extremities, and pains in the legs. As a result of treatment by intramuscular injections of Betaxan, these symptoms disappeared within a short time.

Gæhtgens (1936) recorded marked improvement after eight injections of Betaxan in a case of *traumatic neuritis* following parturition. A similar result was obtained by Schwochow (1937) in a case of peripheral neuritis chiefly involving the lower extremities of a woman who had had a stillbirth.

Recent investigations have shown that in *alcoholic polyneuritis*, which has for many years been regarded as the result of a toxic action of alcohol on the peripheral nerves, a deficiency of Vitamin B 1 is the important ætiological factor. (Joliffe and Colbert, 1936).

While it has been found that in many or all cases there is an estimated inadequate intake of the antineuritic vitamin (Joliffe, Colbert and Joffe, 1936), it seems probable that a defective absorption also plays a large part in producing a hypovitaminosis. In a recent paper by Thompson (1937), a causal relationship is postulated between the incidence of polyneuritis among alcoholic addicts and the amount of free hydrochloric acid in the stomach. The considerations upon which this assumption is based are, firstly, the well-known tendency of regular alcoholic excesses to result in a chronic gastritis with a hypochlorhydria or achlorhydria, and, secondly, the readiness with which Vitamin B 1 is destroyed in an alkaline medium, particularly in the presence of alcohol. It is suggested that, where such an achlorhydria exists, the Vitamin B 1 ingested is inactivated in the alkaline small intestine. These observations have a practical bearing in that they illustrate the importance of ensuring the absorption of Vitamin B 1 by parenteral administration in the treatment of alcoholic polyneuritis, polyneuritis of pregnancy, or in any state of hypovitaminosis B 1, where it is suspected that a gastro-intestinal dysfunction may operate.

Very favourable results have been achieved by this treatment of polyneuritis in chronic alcoholics even when their customary consumption of spirits is in no way restricted. In one group of patients whose daily ration of whisky varied from a pint to a quart, the administration of Vitamin B 1 resulted in improvement in every case (Strauss, 1935).

Other conditions in which there may be a defective assimilation of the vitamin are *pernicious vomiting from any cause, functional hypochlorhydria, diarrhœa, and tube-feeding* through an intestinal fistula.

ESTIMATION OF DEFICIENCY

Attempts are being made to arrive at a simple method of estimating the intake of Vitamin B 1 by examinations of urine and blood.

Harris and Leong (1936) have devised a method which involves shaking the urine in the presence of ' acid clay ' which has the property of adsorbing the vitamin. Unit quantities of the activated acid clay are then fed to rats in whom a bradycardia has been produced by a Vitamin B 1-free diet. The time taken for the restoration of the normal rate is compared with standards based on International units.

It would appear that the amount of Vitamin B 1 excreted in the urine is about 5 to 8 per cent. of that ingested. Any decrease in the amount ingested is rapidly reflected in the urinary output. When a normal human subject was fed on a B 1-free diet for three days, the output fell from a normal level of 51 International units to 10 International units per diem. On the fourth day a diet calculated to contain 490 International units was instituted, and it was found that the output remained subnormal for some time, indicating a serious depletion of B 1 reserves.

A further significant observation was that, where a small urinary output indicated a subnormal intake, and where the intake was subsequently raised to a normal level, a lag occurred before the output showed an equivalent increase. This phenomenon would seem to indicate that the initial increase was at once taken up by the tissues until a saturation point was achieved.

Another method of estimating deficiencies upon which work is now in progress involves estimation of the concentration of Vitamin B 1 in the blood, by calculating its catalytic action on the growth of the mould already referred to. (Peters, 1936).

EMPIRICAL USE OF VITAMIN B 1

IN CONDITIONS NOT DUE TO A PROVEN DEFICIENCY.

Considerable success has attended the empirical use of Vitamin B 1 in the treatment of conditions presenting symptoms which bear a resemblance to those caused by a known lack of the vitamin. Thus, Vorhaus, Williams and Waterman (1935), treated one hundred unselected cases of *multiple and localised neuritis* of diverse ætiology by administration of Vitamin B 1. Of this series, only eight failed to show improvement, forty-four enjoying complete cures, while the remaining forty-eight were improved.

Of eight other patients with *anorexia* and *intestinal hypotonia*, six were cured by treatment with Vitamin B 1. The same authors (1935-36) state that the administration of Vitamin B 1 to proven cases of *diabetes mellitus* resulted, in six out of eleven instances, in an increased carbohydrate utilisation.

Ruschke (1936) and von Lobenstein (1936) have reported similar favourable results in the treatment of *neuritis*. The latter used Betaxan in a case of severe *polyneuritis* with paralytic manifestations which had failed entirely to respond to other methods of treatment. The patient received sixteen intramuscular and three intravenous injections at intervals of two days and was subsequently discharged in good health and free from pain. The same author also quotes six other cases successfully treated with Betaxan, two of *brachial plexus neuritis*, two of *radial neuritis*, and two of partial *paralysis of the facial nerve*.

Acute polyneuritis in a 34-year-old patient, with unusually severe pain in nearly all the nerve trunks, was described by Fetscher

(1936). Ten injections of Betaxan were sufficient to bring about a freedom from pain. A patient cited by Ebermaier (1937) suffering from neuritic pains in the ulnar region of the right hand was cured after a course of five injections. Hesse (1936) obtained rapid and satisfactory results in the treatment by Betaxan injections of *crural neuritis*, a condition commonly occurring among mountain dwellers. One intractable case became ambulant after six such injections.

It has been stated (Kühnau, 1937) that certain of the heavy metals, notably thallium, affect the action of vitamins and produce an avitaminosis. Heimann (1936) successfully treated neurological disturbances due to *thallium poisoning* by intramuscular administration of Betaxan. Gallowitsch (1937) obtained similar results in a case of *arsenical polyneuritis*. Kühnau has also suggested that the neuritis occurring in *lead poisoning* is associated with a defective assimilation of Vitamin B 1. In *occupational neuritis* the use of Betaxan has also been found (Fetscher, 1936) to constitute a reliable method of treatment.

A violinist with a neuritis of the left elbow recovered full capacity for work after twelve injections, while fifteen injections completely cured a neuritis of the flexor nerves of the left forearm in a pianist. A right ulnar neuritis in another musician disappeared after only three injections.

Other forms of occupational neuritis which have been similarly treated include those found among tailors, stenographers and dairymen.

Ruschke (1936) and Schwochow (1937) both found Betaxan to be effective in the treatment of *post-influenzal neuritis*, the former obtaining a successful result after seven injections in one case and ten in another, while, in a patient with a *nicotine neuritis*, considerable relief was experienced after two injections.

In the treatment of *sciatica*, Ruschke (1936), Schwochow (1937), Fetscher (1936), von Lobenstein (1936) and Haberkamp (1937) have unanimously reported excellent results following the use of Betaxan. It is sufficient to quote two illustrative cases.

One patient with a sciatica of several months' standing was free from pain after six injections (Ruschke). The other was free from pain after three injections and had recovered normal movements by the sixth. (Fetscher).

The following cases illustrate the results obtained by the treatment of *post-diphtheritic paralysis* with Betaxan.

A child of nine with paralysis of accommodation, weakness of both arms and legs, and diminished tendon reflexes recovered after daily injections of Betaxan for a period of three weeks, while a child of twelve with similar symptoms was considerably improved (Neumann). A moribund child of four years with diaphragmatic paralysis was successfully treated with Betaxan (Bennholdt - Thomsen, 1936). In an adult patient with pseudo-tabes, extreme difficulty in swallowing (paralysis of recurrent laryngeal nerve) and a rapidly advancing paralysis of the diaphragm, the administration of Betaxan averted a fatal termination and brought about a striking improvement (Knapp, 1937). In a patient of thirty-five with post-diphtheritic weakness, a course of twelve Betaxan injections succeeded after other methods of treatment had resulted in failure.

Another of the many indications of the use of Betaxan is furnished by *trigeminal neuralgia.*

Böhm (1936) describes a case in which attacks of pain had extended over a period of four years and were of extreme severity. Alcohol injections and dental treatment had been adopted without improvement. After four injections of Betaxan considerable relief was experienced, and after seven injections there was a complete disappearance of symptoms.

Severe *intercostal neuralgia* is yet another condition which has been found to yield to treatment with Betaxan (Ruschke).

Subacute combined degeneration of the cord, which is now considered to be related to a chronic deficiency of the Vitamin B complex (particularly Vitamin B 1) has been treated, with encouraging results, by the administration of Betaxan.

A patient with a red cell count of 2,200,000 after treatment (Lasch, 1936) with a liver preparation showed an increase to 3,600,000 red cells. No improvement occurred in the neurological symptoms. A course of ten injections of Betaxan was instituted, after which the patient was able to support himself on his legs unaided. After a second course, even short walks were possible. The third course resulted in the disappearance of neurological signs, while the simultaneous administration of Campolon brought the red cell count to within normal limits. Müller-Deham (1937) describes the case of a patient who had received liver-therapy and had been bed-ridden for six years but who was able to walk after six Betaxan injections. Bergel (1936), Neumann (1935), Böhm (1936) and Molnar (1937) have obtained corroborative results.

It has been reported (Neumann, 1935) that a woman of twenty-nine with *disseminated sclerosis* showed a definite decrease of spasticity following a course of twelve Betaxan injections. Molnar and Böhm, however, could observe no improvement in their cases. Nevertheless, in view of the absence of any satisfactory treatment for this condition, Betaxan would seem to be worth a more extensive trial.

In *tabes dorsalis* Neumann found that relief from severe shooting pains was afforded by a course of five Betaxan injections.

H. J. Lauber (1936) demonstrated that the administration of Vitamin B 1 accelerated the rate of *healing of fractures* in 60 per cent. of cases.

Freudenberg (1937) has drawn attention to the use of Betaxan in the treatment of unduly protracted coma arising from the *insulin-shock* treatment of schizophrenia. Patients who could not be

roused by 400 ccm. of 50 per cent. dextrose solution regained consciousness within twenty to thirty minutes of the administration of 1,000 international units of Betaxan.

Promising results were obtained by Carmalt-Jones (1932), by the use of a Vitamin B 1 preparation in the treatment of *œdema*, particularly where the œdema was associated with pernicious anæmia.

Other conditions in which the administration of Betaxan appears to have exerted a favourable effect are *rheumatism* associated with anorexia (Stepp, Kühnau, and Schroeder, 1937), and *gastro-enteritis* (Koch, 1937).

CLASSIFICATION OF CLINICAL INDICATIONS

FOR THE USE OF 'BETAXAN'

A WHERE THERE IS A KNOWN DEFICIENCY OF OR FAILURE TO ASSIMILATE VITAMIN B 1.

1. Beri-beri.
2. Polyneuritis of Pregnancy.
3. Alcoholic Polyneuritis.

B WHERE THERE *MAY BE* A DEFICIENCY OF OR FAILURE TO ASSIMILATE VITAMIN B 1.

1. Neuritis. Neuralgia. Sciatica. Myalgia.
2. Anorexia. Hypochlorhydria.
3. Atonic Constipation.
4. Retarded Growth and Poor Nutrition in Infants and Children.
5. Dyspnœa. Palpitations. Œdema.
6. Special Diets, e.g. Sippy, Ketogenic, Weight-reducing.
7. Delayed Union of Fractures.

C WHERE AN INCREASED VITAMIN B 1 REQUIREMENT MAY RESULT IN A RELATIVE DEFICIENCY.

1. Pregnancy. Lactation. Prolonged Muscular exertion.
2. Hyperthyroidism.
3. Febrile diseases.
4. High Carbohydrate diets.
5. Diabetes Mellitus.

D WHERE FAVOURABLE RESULTS HAVE ATTENDED THE EMPIRICAL USE OF VITAMIN B 1.

Disseminated Sclerosis. Subacute Combined Degeneration. Tabes Dorsalis.

MODE OF ADMINISTRATION AND DOSAGE

Betaxan may be administered orally or parenterally. In view of the possibility of failure of absorption by the oral route, parenteral administration is advisable when practicable. The usual dose is 1 to 2 ampoules injected intramuscularly. One ampoule contains 2 mgm. of synthetic Vitamin B 1, which represents, roughly, 1,000 International units. Injections should be given daily and may be continued for long periods without fear of cumulative effects. Should Betaxan be given orally, the usual dose is from 1 to 3 tablets three times a day. One tablet contains 1 mgm. of Vitamin B 1.

A more intensive scheme of dosage has been recommended by some physicians who have given doses of 10 mgm. daily either orally or parenterally. *This dosage can be prescribed quite safely without fear of toxic effects.

* Special ' forte ' ampoules containing 5,000 international units per c.c. are available for this purpose.

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